REMARKS

Currently, claims 1, 4-6, 9, 10, 16, and 94-98 are pending. Claims 94, 95, and 97 are withdrawn. Claim 99 has been added. Support for claim 99 can be found throughout the specification and, for example, at ¶ 97 of the published application. Upon entry of this amendment claims 1, 4-6, 9, 10, 16, 96, 98, and 99 are subject to examination. No new matter has been added. Applicants expressly reserve the right to present additional claims in further applications. All amendments and cancelations are made without prejudice or disclaimer.

Objections

Claim 1 is objected to because of the recitation "inhibiting by RNA interference inside the eye." The Office alleges that the recitation "is somewhat awkward inasmuch as there is no object for the gerund 'inhibiting.' That is, the claim does not explain what exactly the composition is inhibiting." (Office Action, page 4). Applicants respectfully assert that claim 1 was clear, however, solely in order to further prosecution Applicants have amended claim 1 to recite that the compound inhibits the mRNA expression of SEQ ID NO: 3.

In view of the foregoing, Applicants respectfully request that objection to claim 1 be withdrawn.

35 U.S.C. 112, First Paragraph, Enablement Requirement

Claims 4-6 and 10 are rejected under 35 U.S.C. § 112, enablement, as allegedly failing to comply with the enablement requirement. The Office alleges that "apart from this disclosure, however, neither the specification nor the prior or post-filing art teaches or suggest any link between the abnormal expression of ...SEQ ID NO: 3 and any other eye disease" (Office Action, page 5). The Office alleges that there is no evidence in the "prior art or the specification of any correlation between the aberrant expression of PDE6B and any of the disorders recited in claims 4-6 or 10." (Office Action, page 5). The Office alleges because that because there are allegedly no working examples and allegedly no identifiable nexus between the inhibition of SEQ ID NO: 3 "it is reasonable to question the objective truth of the assertions in the claims that the administration of an interfering dsRNA targeting SEQ ID NO: 3 may be used to treat each of

the disorders recited" in claims 4-6 and 10. (Office Action, page 6). Applicants respectfully disagree.

Claims 4-6 and 10 are enabled because one of skill in the art would not need to use undue experimentation to practice the claimed methods. The Office has failed to adequately question the enablement because the Office has failed to provide sufficient evidence to reasonably question the objective truth of the specification and the claims. The M.P.E.P. § 2164.04 states

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

The court further explained "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to ***back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement***. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." (M.P.E.P § 2164.04 (quoting *In re Marzocchi* 439 F.2d at 224, 169 USPQ at 370)). (emphasis added). Here, the Office has not backed up any of its assertions with any acceptable evidence or reasoning.

The Office's only evidence is that there is a lack of working examples. The Office alleges that there is an unpredictability in the art but then fails to supply any evidence demonstrating the alleged unpredictability. Therefore, the Office has not backed up its assertion that the field is unpredictable with anything more than a conclusory statement. Conclusory statements are not sufficient evidence to question the objective truth of the present application. In contrast, the present specification and the claims have demonstrated the delivery and the inhibition of mRNA expression in the eyes. The specification states that SEQ ID NO: 3 can be inhibited and that it can be inhibited in the eye to treat disorders of the eye and the underlying conditions as they are described in claims 4-6 and 10.

The Office repeatedly asserts that there is no other reference demonstrating that SEQ ID NO: 3 is linked to an eye disease. For example, the Office states that the "prior or post-filing art" allegedly does not teach or suggest any link between the abnormal expression of SEQ ID NO: 3 and any other eye disease." (Office Action, page 5). The Office alleges that "A review of the ... prior art, fails to find a single working example" and that "the prior art" does not establish any nexus between the inhibition of SEQ ID NO: 3 and the treatment of each of these diseases as they are recited in claims 4-6 and 10. (Office Action, page 6). The Office appears to be looking for confirmation that the claimed invention is enabled. Whether or not a claim is enabled does not depend upon the existence of other art confirming the enablement of a claim. Rather, the claim is enabled unless the Office presents sufficient evidence to question the objective truth of the specification and the claims. (See M.P.E.P. § 2164.04). Here, the Office has not shown that the specification can be objectively questioned.

The Office's has not provided any evidence other than mere conclusory statements to show that the art is unpredictable, to demonstrate the quantity of experimentation that may be needed, to show the state of the prior art or the level of one of ordinary of skill. The only statement that the Office makes is that the claims would require undue experimentation because it would require "trial and error experimentation to use the claimed invention commensurate with the claims scope." (Office Action, page 6). Trial and error, however, is not the same as undue experimentation. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." (M.P.E.P. § 2164.01). "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *Id.* The Office has failed to show that any experimentation would be required, and that even if some experimentation would be necessary that it would be undue. The Office has failed to show that undue experimentation would be required because the Office has failed to supply sufficient evidence to challenge the enablement of the claims.

Accordingly, the claims are enabled because one of skill in the art using the specification would not require undue experimentation to practice the claimed invention.

Rejection under 35 U.S.C. § 103

Claims 1, 9, 16, 96 and 98 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of U.S. Patent No. 5,814,620 to Robinson et al. (hereinafter "Robinson"), U.S. Patent No. 5,498,521 to Dryja et al., (hereinafter "Dryja"), Weber et al., Nucleic Acids Res. 19: 6263-6268 (1991) (hereinafter "Weber"), Epstein et al., Methods: A Companion to Methods in Enzymology 14:21-33 (1998) (hereinafter "Epstein"), Collins et al., Genomics 13 (3): 698-704 (1992) (hereinafter "Collins") U.S. Patent Publication No. 2004/0259247 to Tuschl et al., (hereinafter "Tuschl"); Bass, Nature 411: 428-429 (2001) hereinafter "Bass."; U.S. Patent No. 7,148,342 to Tolentino et al, hereinafter "Tolentino", and U.S. Patent Publication No. 2002/0054902 to Pardridge, hereinafter "Pardridge". Applicants respectfully disagree.

The crux of the Examiner's arguments rest solely on the "equivalence" of antisense molecules and siRNA in their therapeutic use. However, the Examiner acknowledges that they are structurally distinct and, most importantly, operate via different mechanisms. The MPEP § 2183 states that a *prima facie* case for equivalence can only be found where the element "performs the function specified in the claim." As amended in the previous office action response, the claims recite that the siRNA operate via RNA interference. As admitted in the Office Action mailed July 15, 2008, antisense does not induce interference. Therefore, according to the MPEP, antisense is not an equivalent since it functions differently than siRNA because they operate differently.

Without attempting to belabor the point, the Examiner is respectfully directed to the factors that should be examined to determine equivalence according to the MPEP § 2183(A-D), none of which support a finding of equivalence:

> *(A) [Does] the prior art element perform[s] the identical function specified in the claim in substantially the same way, and produce[s] substantially the same results as the corresponding element disclosed in the specification?*
>
> Response: those of ordinary skill in the art recognize that antisense does not perform an identical function (i.e., antisense does not create RNA interference), does not operate in substantially the same way (i.e., antisense does not form a RISC silencing complex), and does not produce substantially the same results (i.e., antisense is generally regarded as unreliable and is less effective than RNA interference).

(B) [Would] a person of ordinary skill in the art would have recognized the interchangeability of the element shown in the prior art for the corresponding element disclosed in the specification?

Response: there has been no evidence presented that antisense and siRNA are interchangeable. Simply, because siRNA and antisense can be broadly described as gene therapy does not make the molecules interchangeable, especially since they operate via different biochemical mechanisms.

(C) [Are] there insubstantial differences between the prior art element and the corresponding element disclosed in the specification?

Response: siRNA and antisense are substantially distinct in structure and operate via different biochemical mechanisms. Such differences are clearly not insubstantial.

(D) [Is] the prior art element is a structural equivalent of the corresponding element disclosed in the specification?

The structure of antisense (single stranded DNA) is obviously different than siRNA (double stranded RNA) and thus not equivalent.

The Office alleges that "siRNAs and antisense oligos are art-recognized equivalents" because they are techniques used to prevent the expression of particular genes. (Office Action, page 12). The Office, alleges that this makes the two types of compounds "equivalents" in the art citing to M.P.E.P 2144.06. Applicants, respectfully disagree that the Office has shown that they are art-recognized equivalents.

M.P:E.P. 2144.06 states "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on . . . the mere fact that the components at issue are functional or mechanical equivalents." Here, the Office is relying solely on the fact that siRNA and antisense are functionally equivalent because they both lead to the decrease in mRNA expression. This does not make siRNA and antisense equivalent. Equivalence must be recognized in the prior art. (M.P.E.P. 2144.06) The Office has failed to show that antisense directed at SEQ ID NO: 3 is equivalent to siRNA targeted to SEQ ID NO: 3. The Office only provides references demonstrating that siRNA was known and that antisense was known and, therefore, siRNA against the target was obvious because one of skill in the art can substitute one equivalent for another. But there is nothing in the cited references that demonstrates the siRNA of the claimed invention is equivalent to anything in the cited references. The Office cites, in part, Tuschl to show equivalence. The Tuschl statements, however, are specific to the examples provided in the Tuschl reference. The

Office has not explained why the conclusions about PKR as they refer to in Tuschl can be extrapolated to the presently claimed invention. Therefore, there is no general recognition in the art that all siRNA is equivalent to antisense.

Accordingly, the Office has not established that there was at the time the application was filed an art-recognized equivalent targeting SEQ ID NO: 3 and that the present invention is a mere substitution. Because the present invention is not a mere substitution the claimed invention is not obvious.

The Office also alleges that the present invention is obvious because it "Applicant has used routine methods to confirm what was already believed to be true." (Office Action, page 15). It has not been shown or suggested that siRNA targeted to SEQ ID NO: 3 could be used to treat an eye disorder by the prior art. None of the reference suggest this method. This is in contrast to *PharmaStem Therapeutics v. ViaCell*, 83 USPQ2d 1289, cited by the Office, where the art suggested the method but did not actually carry out the method and the inventors in that suit confirmed what was already suggested. The present invention, is more than a mere valuable contribution is an unobvious invention that does more than confirm what was already expected.

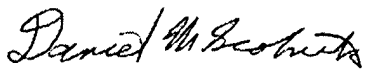
Thus, any *prima facie* case for obviousness made by the Examiner is effectively rebutted, and the Examiner's rejections based on the combined teachings of cited references should be withdrawn. For at least the reasons set-forth above, reconsideration and withdrawal of the Examiner's rejection is respectfully requested.

CONCLUSION

Applicant has timely filed this response. In the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Should the Examiner have any questions or comments, or need any additional information from Applicants' attorney, he is invited to contact the undersigned at his convenience.

Respectfully submitted,



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